
Non-Interventional Study Protocol

Study Protocol Number	EMR200136_597
Title	A Phase IV, prospective, multicenter, open label, uncontrolled, non-interventional, single arm study to measure treatment satisfaction of multiple sclerosis (MS) patients on Rebif® after discontinuing initial first-line treatment
Study acronym/Short title	MESTRE–MS (ME asuring S atisfaction of T reatment with RE bif after initial treatment of MS)
Protocol version identifier	Version 2.0
Date of last version of protocol	07 Oct 2016
Replaces Study Protocol Version	Version 1.0/20 May 2016
Active substance	International Nonproprietary Name (INN): Interferon beta-1a; Pharmacotherapeutic Group: Immunostimulants; Anatomical Therapeutic Chemical (ATC) Code: LO3AB07
Medicinal product	Rebif
Marketing authorisation holder (MAH)	Merck Serono Europe Limited
Research question and objectives	<p>The purpose of this study is to investigate treatment satisfaction of MS patients, who have discontinued first-line MS oral or injectable MS medication, and have initiated treatment with Rebif.</p> <p>Primary objective</p> <ul style="list-style-type: none">• To determine the level of treatment satisfaction as measured with the Treatment Satisfaction Questionnaire for Medication Version II (TSQM v II), in relapsing remitting MS (RRMS) patients who have discontinued their initial oral or injectable MS treatment, and have initiated treatment with Rebif. <p>Secondary objectives</p> <ul style="list-style-type: none">• To evaluate the change in annualized relapse rate (ARR) in patients changing from initial oral or injectable forms of treatment to Rebif

- To assess therapy adherence to Rebif
- To determine the change in quality of life with Multiple Sclerosis International Quality of Life Questionnaire (MusiQoL) between Baseline, Month 6 and Month 12
- To document the reasons for discontinuation of initial MS treatment
- To evaluate the potential correlations between the following measurements: TSQM v II, ARR, adherence, reasons for discontinuation, MusiQoL and TSQM v II subscales
- To assess the difference between TSQM v II subscales between Baseline, Month 6 and Month 12.

Countries of study

The study will be conducted in approximately 33 centers across Europe region in Belgium, Switzerland and the Netherlands.

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2 List of Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ARR	Annualized Relapse Rate
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
DMD	Disease Modifying Drug
eCRF	Electronic Case Report Form
EDSS	Expanded Disability Status Scale
HCP	Health Care Professional
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFN β	Interferon beta
IRB	Institutional Review Board
MAH	Marketing Authorisation Holder
MS	Multiple Sclerosis
MusiQoL	Multiple Sclerosis International Quality of Life Questionnaire
Q1	First Quartile
Q3	Third Quartile
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SmPC	Summary of Product Characteristics
TSQM v II	Treatment Satisfaction Questionnaire for Medication Version II

3 Responsible Parties

Coordinating Investigator of the Protocol

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3.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the study at his/her site. He/She will ensure that the study is performed in accordance with the protocol and will ensure the quality and integrity of data, following all applicable international and national guidelines.

This non-interventional study will not interfere with treatment prescription by Investigators. Accordingly, the Investigator will decide in advance the best therapeutic strategy for each patient according to current practice, regardless of the potential participation of this patient in the study. Subsequently, if the prescribed treatment is in line with the study protocol, the Investigator will consider the possibility of including the patient in the study.

The Investigator is responsible for adverse reaction (AR) recording and reporting, as specified in Section [11](#).

4

Abstract

Title	A Phase IV, prospective, multicenter, open label, uncontrolled, non-interventional, single arm study to measure treatment satisfaction of multiple sclerosis (MS) patients on Rebif® after discontinuing initial first-line treatment
Study acronym/Short title	MESTRE–MS (ME asuring Satisfaction of Treatment with RE bif after initial treatment of MS)
Study Protocol Date / Version	07 Oct 2016/Version 2.0
Rationale and background	<p>The purpose of this study is to investigate treatment satisfaction in MS patients, who have discontinued first-line MS oral or injectable MS medication, and have initiated treatment with Rebif. MS patients who are starting their first treatment for MS currently can be treated with various oral or injectable medications. When solely considering the route of administration of these medications it may appear that the oral treatments are more patient friendly and convenient than the injectable ones. In addition, certain weekly or daily first-line injection treatments may be preferred over thrice weekly injections for unknown reasons. In clinical trials, discontinuation rates due to adverse events (AEs) of dimethyl fumarate (Tecfidera®) and of teriflunomide (Aubagio®) treated patients is 16% in both DEFINE and TENERE studies, respectively. Furthermore, injectable treatment discontinuation varies between 14% and 47%. It is important for patients to optimally utilize first-line MS treatment options before escalating therapy to more potentially dangerous second line therapies such as natalizumab, fingolimod or alemtuzumab.</p> <p>This Phase IV clinical study is being proposed to support decision making for health care professionals (HCPs) and patients who have decided to initiate MS treatment, and use arguments of patient friendliness and convenience for their decision. Therefore, in this study treatment satisfaction of Rebif is measured in MS patients who have discontinued their initial MS treatment, and who have decided to start Rebif as their follow-up treatment. Currently there is no information describing the experiences with discontinuation of oral or injectable medication and the initiation of the injectable therapy Rebif. This information is crucial for HCPs and patients to be able to make a well informed decision on what to expect of their treatment. In this study, by measuring treatment satisfaction before and after Rebif treatment we aim to evaluate the difference in treatment satisfaction (as</p>

	<p>perceived by the patient), reasons to stop initial treatment, and experience after alternative treatment initiation.</p> <p>The clinical trial will contribute to the vast amount of data there is of Rebif. This study will add the additional data on the perception of treatment convenience and reasons for discontinuation of oral or injectable first-line treatment.</p>
Research question and objectives	<p>Primary objective</p> <ul style="list-style-type: none"> • To determine the level of treatment satisfaction as measured with the Treatment Satisfaction Questionnaire for Medication Version II (TSQM v II), in relapsing remitting MS (RRMS) patients who have discontinued their initial oral or injectable MS treatment, and have initiated treatment with Rebif. <p>Secondary objectives</p> <ul style="list-style-type: none"> • To evaluate the change in annualized relapse rate (ARR) in patients changing from initial oral or injectable forms of treatment to Rebif • To assess therapy adherence to Rebif • To determine the change in quality of life with Multiple Sclerosis International Quality of Life Questionnaire (MusiQoL) between Baseline, Month 6 and Month 12 • To document the reasons for discontinuation of initial MS treatment • To evaluate the potential correlations between the following measurements: TSQM v II, ARR, adherence, reasons for discontinuation, MusiQoL and TSQM v II subscales • To assess the difference between TSQM v II subscales between Baseline, Month 6 and Month 12.
Study Design	<p>This is a prospective, multicenter, open label, uncontrolled, non-interventional, single arm study to measure treatment satisfaction of RRMS patients on Rebif after discontinuing initial first-line treatment.</p> <p>This study consists of three visits:</p> <ul style="list-style-type: none"> • Visit 1: Baseline • Visit 2: Month 6 • Visit 3: Month 12 <p>This study will enroll RRMS patients who have discontinued their oral or injectable first-line MS medication and have decided to initiate</p>

	<p>subcutaneous Interferon beta-1a (IFNβ-1a) (Rebif) treatment before Baseline measurements. MusiQoL and TSQM v II will be measured at Baseline, Month 6 and Month 12. Relapses and adherence will be assessed at Month 6 and Month 12. Adherence to Rebif therapy will be collected electronically using RebiSmart 2.0.</p> <p>Since this is a non-interventional study, there will not be any study required clinical interventions and laboratory assessments.</p>
Population	<p>RRMS patients who have discontinued their initial MS treatment and for whom MS treatment is required according to the decision of the HCP and patient.</p> <p>Inclusion Criteria:</p> <p>The patient can be included when the patient</p> <ul style="list-style-type: none"> • Is male or female, 18 to 65 years of age (both inclusive), at the time of informed consent • Is diagnosed with RRMS according to McDonald criteria 2010 • Has discontinued treatment with dimethyl fumarate (Tecfidera), teriflunomide (Aubagio), glatiramer acetate (Copaxone®), intramuscular IFNβ-1a (Avonex®), pegylated interferon (Plegridy®), subcutaneous IFNβ-1b (Betaferon®) or fingolimod (Gilenya®) within 6 months prior to Visit 1 • Is currently treated with Rebif using RebiSmart 2.0, for a maximum of 6 months prior to Visit 1 • Has a score on the Expanded Disability Status Scale (EDSS) between 0 to 5.0 inclusive • Is willing and able to give informed consent. <p>Exclusion Criteria</p> <p>The patient cannot be included when the patient</p> <ul style="list-style-type: none"> • Has known planned surgical procedures at the time of the informed consent that will prevent adherence to treatment with Rebif through RebiSmart 2.0 • Is diagnosed with primary progressive, secondary progressive, or progressive relapsing MS • Is pregnant or lactating, or planning to become pregnant • In the opinion of the Investigator has significant renal or hepatic impairment or other significant disease (e.g., cognitive or visual impairment) that would compromise adherence and completion of the study

	<ul style="list-style-type: none"> • Reports any reason that he/she cannot complete the 1 year study • Has a history of hypersensitivity to natural or recombinant interferon, or any other component of the formulation • Is contraindicated for the treatment with subcutaneous IFNβ-1a therapy as per summary of product characteristics or currently approved specific country product information • Has any other factor that in the opinion of the Investigator would make the subject unsuitable for participation in this study • Have significant psychiatric symptoms that, in the opinion of the Investigator, would impact patient ability to comply with treatment recommendations.
Variables	<p>The variables that will be evaluated in this study include demographics, MS history, prior and current medication, pertinent medical history, treatment satisfaction score determined with TSQM v II, ARR, treatment adherence, quality of life determined with MusiQoL questionnaire, reasons for discontinuation of previous therapy and AEs.</p> <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Treatment satisfaction score determined with TSQM v II from Baseline to Month 6 and to Month 12. <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • ARR (after 12 months of Rebif treatment) • Adherence (after 6 and 12 months of Rebif treatment) • MusiQoL (compare Baseline with after 6 and 12 months of Rebif treatment) • Reason/s for discontinuation of initial MS treatment (oral or injectable). <p>Additional Secondary Endpoints:</p> <ul style="list-style-type: none"> • Correlation between TSQM v II and ARR; TSQM v II and adherence; TSQM v II and reason for discontinuation • Correlation between MusiQoL and ARR; MusiQoL and adherence; MusiQoL and reason for discontinuation • Correlation between TSQM v II subscales and adherence • Correlation between TSQM v II subscales and reasons for discontinuation • Difference between TSQM v II subscales at Baseline and after 6 and

	<p>12 months of Rebif treatment</p> <ul style="list-style-type: none"> • ARR before study entry compared to ARR at study end • Association between ARR and treatment adherence.
Data Sources	<p>The source of information will be data collected from the medical records, prescription records, laboratory reports and/or routine interview of patients. Data will be entered into the electronic case report form by the Investigator site staff.</p>
Study Size	<p>133 patients diagnosed with RRMS will be enrolled (63 in the Netherlands, 40 in Switzerland and 30 in Belgium).</p>
Sample size justification	<p>A sample size of 106 subjects will be required to have 85% power to detect at least an 8 point difference in mean TSQM scores between Baseline and Month 6 or Month 12 measurements, with the standard deviation of 27.5 and a two sided significance level of 5%. Assuming a 20% dropout rate, approximately 133 patients will be enrolled into the study in the Netherlands, Switzerland and Belgium.</p>
Data Analysis	<p>Statistical analysis will be mainly descriptive. Descriptive statistics (n, mean, standard deviation, median, first quartile [Q1], third quartile [Q3], minimum, maximum) will be provided for continuous variables. Frequencies and percentages will be presented for categorical and ordinal variables. Where appropriate, 95% confidence intervals (CIs) will be presented.</p> <p>All analyses will be performed on subjects who received at least one dose of Rebif following enrollment in the study.</p> <p>Primary Endpoint analysis:</p> <p>A paired two-sided t-test of the global satisfaction score (TQSM score) will be used to test the null hypothesis that there is no difference in the global satisfaction score (TQSM score) between 6, 12 months and Baseline. The corresponding 95% two-sided CI will be presented.</p> <p>Secondary Endpoint analysis:</p> <p>ARR and its associated 95% CI before study entry and after 12 months of Rebif treatment will be summarized overall and by previous MS therapy.</p> <p>Reasons for discontinuation of previous therapy and adherence after 6 and 12 months of Rebif treatment will be summarized descriptively and overall.</p>

	<p>Changes in MusiQoL after 6 and 12 months of Rebif treatment versus Baseline will be analysed using same methodology as for Primary Endpoint.</p> <p>Analysis of additional Secondary Endpoints as correlation analysis between TSQM and MusiQoL versus ARR, adherence and reason for discontinuation will be described in the statistical analysis plan.</p>
Milestones	<p>First Patient First Visit (FPFV): September 2016</p> <p>First Patient Last Visit (FPLV): September 2017</p> <p>Last Patient First Visit (LPFV): September 2017</p> <p>Last Patient Last Visit (LPLV): September 2018</p> <p>Database lock: November 2018</p> <p>Final Clinical Study Report: March 2019</p>

5 Amendments

None

6 Milestones

Milestone	Planned date
Start of data collection	September 2016
End of data collection	September 2018
Database lock	November 2018
Final report of study results	March 2019

7 Rational and Background

Multiple sclerosis (MS) is a chronic inflammatory, autoimmune, demyelinating disease that affects the central nervous system (1). Relapsing remitting MS (RRMS) is the most common type of MS, affecting approximately 80% to 85% of all patients with MS, and is characterized by unpredictable acute attacks (known as relapses) accompanied by worsening of symptoms, followed by periods of remission during which there is a full or partial recovery from the deficits acquired during the relapse (2). Relapse activity is associated with an increased risk of disability progression (3), although disability can advance independently of relapse activity (secondary progressive MS) (4). The increasing number of first-line and second-line treatment options, together with the variable course of the disease and patient lifestyles and expectations, makes the therapeutic decision a real challenge (5).

Disease Modifying Drugs and Interferon beta –1a (IFNβ-1a) treatment

Treatment of RRMS typically consists of direct symptom management, brief corticosteroid administration for acute exacerbations, and the regular use of Disease Modifying Drugs (DMDs). Currently approved immunomodulator treatments for RRMS include recombinant beta interferons (IFNβ-1a, Avonex®; IFNβ-1a, Rebif®; IFNβ-1b, Betaferon® and Extavia®) and glatiramer acetate (Copaxone®). Additional first-line immunosuppressant therapies include dimethyl fumarate (Tecfidera®) and teriflunomide (Aubagio®). Natalizumab (Tysabri®), alemtuzumab (Lemtrada®), and fingolimod (Gilenya®) are also available for treatment of MS as second-line therapy in more severe disease (6), while in Switzerland fingolimod can be prescribed as first-line medication.

Interferons are a family of naturally occurring proteins that are produced by eukaryotic cells in response to viral infections and other biological inducers. Human interferons have anti-inflammatory, antiviral and antigrowth properties. They exert their biological effect by binding to specific receptors on the surface of cells, initiating a complex cascade of intracellular events; however the mechanism of action of IFNβ-1a in MS remains unclear.

Rebif is a human IFNβ-1a used for the treatment of MS. The amino acid sequence of Rebif is identical to the natural interferon derived from human fibroblasts. IFNβ-1a is produced by recombinant deoxyribonucleic acid (DNA) technology using genetically engineered Chinese hamster ovary cells into which the human gene has been inserted (7,8).

Rebif Drug information

The currently marketed formulation of Rebif (IFNβ-1a) has been evaluated in a series of well controlled MS studies which have demonstrated that Rebif significantly reduces clinical attack rate, magnetic resonance image lesion activity, accumulation of new lesion burden, and disability progression (9,10,11,12,13). Rebif is the only disease modifying agent for MS available today to have demonstrated efficacy on all four of these efficacy measures in RRMS. Long term data have also demonstrated that Rebif at either 22 mcg or 44 mcg three times a week maintains these clinical benefits in a dose related manner (14,15,16) and that high frequency administration,

i.e., three times a week, at the highest dose available, i.e., 44 mcg, provides more clinical benefit than 30 mcg administered once a week (17).

Existing data show that, overall, Rebif is well tolerated at the doses intended for use in the MS population, namely 44 mcg three times a week administered by the subcutaneous route. The 22 mcg three times a week dosage is recommended for patients who cannot tolerate the high dose. Patients using Rebif are likely to experience the known undesirable effects to interferon, such as influenza-like-syndrome; injection site reaction (from the common mild inflammatory reactions to the uncommon injection site necroses); asymptomatic hepatic enzymes abnormalities, especially alanine aminotransferase elevation; white and red blood cell counts decrease; and skin reactions, usually rash. The majority of adverse reactions (ARs) observed with Rebif is usually mild and reversible, and respond well to dose reductions. Details are disclosed in the currently approved product information (for further information, please see the summary of product characteristics (SmPC) (18).

Since its introduction in the market in 1998, the cumulative exposure to Rebif by end of March 2014 can be estimated to amount to more than 1,259,436 patient-years in the post marketing setting. During 15 years of Rebif's post-marketing surveillance a series of adverse events (AEs) have been identified, such as ARs, including Quincke's edema, anaphylaxis, urticaria, serious cutaneous reactions, including Stevens-Johnson syndrome, hepatitis with or without icterus, or injection site infection and cellulitis, which could be severe, as with any protein therapeutic agent, cases of thrombotic microangiopathy including fatal cases, have been reported during treatment of MS with interferon beta products. Most thrombotic microangiopathy cases presented as thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome. Rebif therapy may induce the formation of antibodies. Despite the full significance of the formation of neutralizing antibodies remains unclear, it may represent an efficacy rather than a safety issue (11,12,13,19,20,21,22,23,24,25).

An electronic, handheld, multidose, autoinjection device that incorporates a dosing history log has been developed to improve the injection experience, patient satisfaction and treatment adherence among patients self-administering subcutaneous IFN β -1a. In a multicentre, international user trial, this device was considered 'very suitable' or 'suitable' for self-injection by 71.6% of patients and 92.2% reported some degree of suitability (26). The incidence of infusion site reactions was decreased with the autoinjector compared to manual injection, coupled with ease of use of the autoinjector, suggest that it could improve compliance, and therefore therapeutic outcomes in some patients (27). Cramer et al., showed the evidence of significant improvements in all subscales of the MS treatment concerns questionnaire, including global patient satisfaction (but with the exception of 'flu-like' symptoms), and all pain measures after patients with MS switched from using the RJ auto injector to the RJII device (28).

Study Rationale

Since MS is a currently incurable, chronic disease, long term DMD therapy is required, necessitating commitment from patients to continue their treatment (29).

Patient's and health care professionals (HCPs) decision for MS treatment frequently is based on subjective perception of convenience.

Some patients may need to discontinue their MS treatment due to lack of efficacy or side effects. At present, there is limited real world information regarding which therapy provides the best clinical response in patients with RRMS following a switch (2).

MS patients who are starting their first treatment for MS currently can be treated with various oral or injectable medications. When solely considering the route of administration of these medications it may appear that the oral treatments are more patient friendly and convenient than the injectable ones. In addition, certain weekly or daily first-line injection treatments may be preferred over thrice weekly injections for unknown reasons. In clinical trials, discontinuation rates due to AEs of dimethyl fumarate (Tecfidera) and of teriflunomide (Aubagio) treated patients are 16% in both DEFINE and TENERE studies, respectively. Furthermore, injectable treatment discontinuation varies between 14% and 47% (20). It is important for patients to optimally utilize first-line MS treatment options before escalating therapy to more potentially dangerous second line therapies such as natalizumab, fingolimod or alemtuzumab.

This Phase IV clinical study is being proposed to support decision making for HCPs and patients who have decided to initiate MS treatment, and use arguments of patient friendliness and convenience for their decision. Therefore, in this study treatment satisfaction of Rebif is measured in MS patients who have discontinued their initial MS treatment, and who have decided to start Rebif as their follow-up treatment. Currently there is no information describing the experiences with discontinuation of oral or injectable medication and the initiation of the injectable therapy Rebif. This information is crucial for HCPs and patients to be able to make a well informed decision on what to expect of their treatment.

The clinical trial will contribute to the vast amount of data there is of Rebif. This study will add the additional data on the perception of treatment convenience and reasons for discontinuation of oral or injectable first-line treatment.

Benefit-Risk Balance

The benefits clearly outweigh the risks of patients treated with Rebif (30). Patients and HCPs decision for MS treatment frequently is based on subjective perception of convenience. Currently there is no information describing the experiences with discontinuation of oral or injectable medication and the initiation of the injectable therapy Rebif. This information is crucial for HCPs and patients to be able to make a well informed decision on what to expect of their treatment. In this study, by measuring treatment satisfaction before and after Rebif treatment we aim to evaluate the difference in treatment satisfaction (as perceived by the patient), reasons to stop initial treatment, and experience after alternative treatment initiation. The current lack of

understanding to which DMD the patients can most optimally be transitioned justifies this study and will provide benefit for the patients.

8 Research Question and Objectives

The purpose of this study is to investigate treatment satisfaction of MS patients, who have discontinued first-line MS oral or injectable MS medication, and have initiated treatment with Rebif.

8.1 Primary Objective

To determine the level of treatment satisfaction as measured with the Treatment Satisfaction Questionnaire for Medication Version II (TSQM v II), in RRMS patients who have discontinued their initial oral or injectable MS treatment and have initiated treatment with Rebif.

8.2 Secondary Objectives

- To evaluate the change in annualized relapse rate (ARR) in patients changing from initial oral or injectable forms of treatment to Rebif
- To assess therapy adherence to Rebif
- To determine the change in quality of life with Multiple Sclerosis International Quality of Life Questionnaire (MusiQoL) between Baseline, Month 6 and Month 12
- To document the reasons for discontinuation of initial MS treatment
- To evaluate the potential correlations between the following measurements: TSQM v II, ARR, adherence, reasons for discontinuation, MusiQoL and TSQM v II subscales
- To assess the difference between TSQM v II subscales between Baseline, Month 6 and Month 12.

8.3 Other Objectives

None

9 Research Methods

9.1 Study Design

This is a prospective, multicenter, open label, uncontrolled, non-interventional, single arm study to measure treatment satisfaction of RRMS patients on Rebif after discontinuing initial first-line treatment.

9.1.1 Design Overview

This is a Phase IV, prospective, multicenter, open label, uncontrolled, non-interventional, single arm study to measure treatment satisfaction of RRMS patients on Rebif after discontinuing initial first-line treatment.

This study will enroll RRMS patients who have discontinued their oral or injectable first-line MS medication like dimethyl fumarate (Tecfidera), teriflunomide (Aubagio), glatiramer acetate (Copaxone) intramuscular INFβ1-a (Avonex), pegylated interferon (Plegridy), subcutaneous INFβ-1b (Betaferon) or fingolimod (Gilenya - if permitted as first-line in the country) and have initiated subcutaneous INFβ1-a (Rebif) before Baseline measurements. Approximately 133 patients will be enrolled at approximately 33 centers in Europe (the Netherlands, Switzerland and Belgium) over a period of 1 year.

The reasons for discontinuing oral or injectable first-line MS treatment in daily clinical practice currently are not well described. Furthermore, the treatment satisfaction of patients who are treated with injectable MS medication after discontinuing oral treatment is unknown. Whether an association between treatment satisfaction or quality of life on the one hand and treatment adherence, ARR and reasons for discontinuation on the other exist also is not known and will be investigated as part of this study.

As part of the secondary measures in this study ARR will be measured, and the potential association between clinical effect and medication change will be investigated. Furthermore, therapy adherence will be measured with RebiSmart 2.0 in MS patients who have discontinued their initial oral or injectable MS treatment and have decided to start Rebif treatment. In order to be able to analyze a broader spectrum of convenience perception and satisfaction of treatment also the MusiQoL questionnaire is completed by the patient and a potential correlation between these quality of life outcomes and clinical measures will be explored.

The study consists of 3 visits including Visit 1 (Baseline), Visit 2 (Month 6) and Visit 3 (Month 12). At Baseline, Month 6 and 12 visits, the TSQM v II and MusiQoL will be measured, and relapses and adherence will be measured at Month 6 and 12 visits. Adherence to Rebif therapy will be collected electronically using RebiSmart 2.0.

The reason for discontinuation of the initial treatment will be requested by the study team and documented in the patient file at the Baseline Visit. The collection of AEs will be a regular part of each visit and will be documented and communicated according to safety policies.

Since this is an observational study to observe the usual practice, there will not be any study required clinical interventions and laboratory assessments.

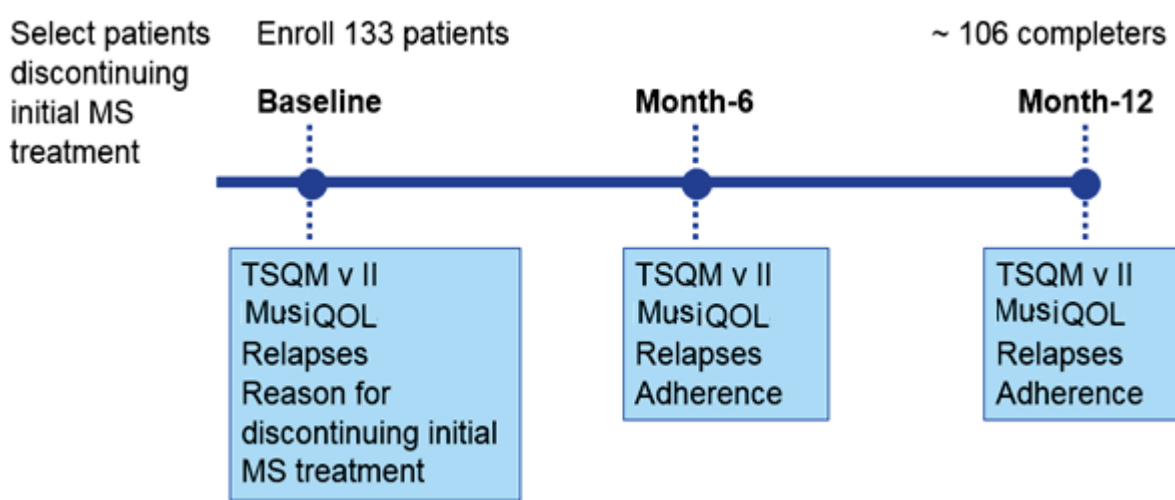
Upon site initiation, each investigator site will enroll subjects who meet the eligibility criteria. Enrollment will be in a consecutive manner until the site enrollment target is reached. The recruitment period is planned to be between September 2016 and September 2017. However, this may be extended if the recruitment target is not met. In this study subjects will be treated with Rebif three times weekly delivered through electronic autoinjector device (the RebiSmart 2.0).

Treatment regimen will be as per Investigators routine practice and in accordance with the licensed SmPC label or currently approved specific country product information.

The study will receive approval from the governing institutional review board (IRB) or independent ethics committee (IEC) when required and in accordance with the ethical regulation of the country.

An informed consent form (ICF) will be signed by the subject, and subjects are free to withdraw at any time without prejudice to their medical care, and that they are not obliged to state their reasons. The diagram below summarizes the study plan (see [Figure 1](#)).

Figure 1 Study Overview



TSQM v II = Treatment Satisfaction Questionnaire for Medication Version II

MusiQoL = Multiple Sclerosis International Quality of Life Questionnaire

MS = Multiple Sclerosis

9.1.2 Endpoints

9.1.2.1 Primary

- Treatment satisfaction score determined with TSQM v II from Baseline to Month 6 and to Month 12.

9.1.2.2 Secondary

Key Secondary Endpoints:

- ARR (after 12 months of Rebif treatment)
- Adherence (after 6 and 12 months of Rebif treatment)

- MusiQoL (compare Baseline with after 6 and 12 months of Rebif treatment)
- Reason/s for discontinuation of initial MS treatment (oral or injectable).

Additional Secondary Endpoints:

- Correlation between TSQM v II and ARR; TSQM v II and adherence; TSQM v II and reason for discontinuation
- Correlation between MusiQoL and ARR; MusiQoL and adherence; MusiQoL and reason for discontinuation
- Correlation between TSQM v II subscales and adherence
- Correlation between TSQM v II subscales and reasons for discontinuation
- Difference between TSQM v II subscales at Baseline and after 6 and 12 months of Rebif treatment
- ARR before study entry compared to ARR at study end
- Association between ARR and treatment adherence.

9.1.2.3 Others

None

9.2 Setting

This study will be conducted in 3 European countries: Belgium, Switzerland and the Netherlands. In this study, the patients diagnosed with RRMS will be enrolled at around 33 sites across Europe region.

9.2.1 Study Population

RRMS patients who have discontinued their initial MS treatment and for whom MS treatment is required according to the decision of the HCP and patient.

The study population will be identified according to the below inclusion and exclusion criteria.

Inclusion Criteria:

The patient can be included in the study when the patient

- Is male or female, 18 to 65 years of age (both inclusive), at the time of informed consent
- Is diagnosed with RRMS according to McDonald criteria 2010
- Has discontinued treatment with dimethyl fumarate (Tecfidera), teriflunomide (Aubagio), glatiramer acetate (Copaxone), intramuscular IFN β -1a (Avonex), pegylated interferon (Plegridy), subcutaneous IFN β -1b (Betaferon) or fingolimod (Gilenya) within 6 months prior to Visit 1

-
- Is currently treated with Rebif, using RebiSmart 2.0 for a maximum of 6 months prior to Visit 1
 - Has a score on the Expanded Disability Status Scale (EDSS) between 0 to 5.0 inclusive
 - Is willing and able to give informed consent.

Exclusion Criteria:

The patient cannot be included when the patient

- Has known planned surgical procedures at the time of the informed consent that will prevent adherence to treatment with Rebif through RebiSmart 2.0
- Is diagnosed with primary progressive, secondary progressive, or progressive relapsing MS
- Is pregnant or lactating, or planning to become pregnant
- In the opinion of the Investigator has significant renal or hepatic impairment or other significant disease (e.g., cognitive or visual impairment) that would compromise adherence and completion of the study
- Reports any reason that he/she cannot complete the 1 year study
- Has a history of hypersensitivity to natural or recombinant interferon, or any other component of the formulation
- Is contraindicated for the treatment with subcutaneous IFN β -1a therapy as per SmPC or currently approved specific country product information
- Has any other factor that in the opinion of the Investigator would make the subject unsuitable for participation in this study
- Have significant psychiatric symptoms that, in the opinion of the Investigator, would impact patient ability to comply with treatment recommendations.

9.2.2 Definition of Study Cohorts and Description of Treatments

There are no study cohorts in this study.

Treatment

Subjects will be treated with Rebif three times weekly, delivered through an electronic autoinjector device (Rebismart 2.0). Treatment regimen will be as per Investigators routine practice and in accordance with the licensed SmPC label or currently approved specific country product information.

9.2.3 Observation Period

Study observation period starts from subjects signing the informed consent and continues until Visit 3 (Month 12). This is estimated to be about 12 months.

9.2.4 Frequency of Assessments

Table 1 summarizes the assessments in each visit. Further details of each are given in the subsequent sections.

This study consists of 3 visits. The study procedure and assessment contents are as follows:

- Visit 1 (Baseline)
- Visit 2 (Month 6)
- Visit 3 (Month 12).

1. Visit 1 (Baseline):

At the initial study visit, the subject will be informed of the study objectives and overall requirements, and written informed consent will be obtained prior to any study specific assessments. The subject will then undergo a brief clinical evaluation to ensure compliance with the inclusion and exclusion criteria to determine the eligibility (see Section 9.2.1).

The following data will be collected at Baseline Visit

- Demographic details including age, gender, height and weight
- Current medical condition and past medical history including concomitant diseases
- MS history (including relapses within 2 years before study entry)
- Prior MS medication
- Prior MS medication related AEs and associated concomitant medications
- Vital signs
- Physical examination
- Neurological examination
- TSQM v II evaluation
- MusiQoL evaluation
- Document reasons for discontinuation of previous MS therapy
- Therapy with Rebif
 - Date of initiation of Rebif

- Initial Dose of Rebif.

Visit 2 (Month 6):

At Visit 2, the treating physician will assess the patient within standard clinical routine practice.

The following data will be collected at Visit 2 (Month 6):

- Vital signs
- Physical examination
- Neurological examination
- Relapse assessment
- TSQM v II evaluation
- MusiQoL evaluation
- Therapy with Rebif
 - Date and dose of Rebif
 - Details of dose adjustments of Rebif if any
- Treatment adherence
- Safety recording and reporting according to Section 11.4 and Section 11.5
- MS medication related AEs and associated concomitant medications

Visit 3 (Month 12):

Visit 3 (Month 12) will be similar to the above described procedure for Visit 2 (Month 6). After the Month 12 visit the study ends.

The following data will be collected at Visit 3 (Month 12):

- Vital signs
- Physical examination
- Neurological examination
- Relapse assessment
- TSQM v II evaluation
- MusiQoL evaluation
- Therapy with Rebif
 - Date and dose of Rebif
 - Details of dose adjustments of Rebif if any

- Treatment adherence
- Safety recording and reporting according to Section 11.4 and Section 11.5
- MS medication related AEs and associated concomitant medications

Table 1 **Schedule of Assessments and Evaluations**

Activity	Visit 1 Baseline	Visit 2 Month 6	Visit 3 Month 12 (End of Study Visit)
Patient Informed Consent	X		
Inclusion/Exclusion Criteria	X		
Demographic information	X		
Medical History / Concomitant diseases / Prior MS medications	X		
Multiple Sclerosis History (including relapses within 2 years before study entry)	X		
MS medication related adverse events and associated concomitant medications	X	X	X
Vital Signs	X	X	X
Physical Examination	X	X	X
Neurological Examination	X	X	X
Relapse Assessment		X	X
TSQM Version II evaluation	X	X	X
MusiQoL evaluation	X	X	X
Document reasons for discontinuation of previous MS therapy	X		
Therapy with Rebif	X	X	X
Evaluation of Adherence to Therapy		X	X
Safety Recording and Reporting		X	X

9.2.5 Withdrawal from the Study

Subjects are free to discontinue the study at any time without giving their reasons. Subjects will be withdrawn from the study for any of the following reasons:

- Subject is lost to follow up
- Occurrence of AE / serious adverse event (SAE), if discontinuation of Rebif is desired or considered necessary by the Investigator and/or the subject

- There is an occurrence of an exclusion criterion
- Subject withdraws consent.
- Discontinuation of Rebif for any reason.

9.3 Variables

The variables that will be evaluated in this study include demographics, MS history, prior and current medication, pertinent medical history, treatment satisfaction score determined with TSQM v II, ARR, treatment adherence, quality of life determined with MusiQoL questionnaire, reasons for discontinuation of previous therapy and AEs.

Primary Endpoint variables:

- Treatment Satisfaction Questionnaire for Medication Version II (31)

TSQM v II was designed as a general measure of treatment satisfaction with medication, suitable for use across a wide variety of medication types and illness conditions. Findings in the development of this questionnaire indicated that the three dimensions on which patients evaluate their medication are: effectiveness, adverse effects and convenience. There was an additional overall satisfaction rating, representing individual balanced judgment across these three specific treatment attributes, potentially most predictive of patient satisfaction and adherence. The final version of the questionnaire is included in [Appendix 1](#).

TSQM v II evaluation will be done at Baseline, Month 6 and Month 12.

Secondary Endpoint variables:

- Annualized relapse rate

ARR is defined as the number of relapses per year and will be calculated using the below formula

$$\text{Annualized Relapse Rate} = (\text{No. of Relapses} / \text{Time on Study}) \times 365.25$$

where, Time on Study (days) = (Date of Study Completion or Date of study discontinuation - Date of first Rebif administration +1)

A relapse is defined as the appearance of a new clinical sign or symptom attributable to MS, or clinical worsening of a previous sign or symptom that had been stable for ≥ 30 days and that persisted for ≥ 24 hours without fever. Relapses are reported by the patient and confirmed by the treating physician. Generally this will occur within several days of the event but is left to the discretion of the neurologist to determine if the event should be recorded as a relapse. Criteria published in the literature describing symptoms accompanied by an increase of at least half a point in the EDSS score, of one point in each of two EDSS functional system scores, or of two

points in one EDSS functional-system score (excluding scores for the bowel–bladder or cerebral functional systems) will be provided to the physician prior to the initiation of the study but the final determination is made by the physician.

Relapse history will be collected at Baseline and relapse assessment will be done at Month 6 and Month 12. ARR before study entry will be compared to ARR at study end.

- Multiple Sclerosis International Quality of Life Questionnaire (MusiQoL) ([32](#))

To evaluate health-related quality of life, all subjects will be asked to complete the MusiQoL.

The MusiQoL is a disease-specific validated 31-item multi-dimensional, self-administered questionnaire. It has nine dimensions:

- Activities of daily living (ADL, 8 items);
- Psychological well-being (PWB, 4 items);
- Symptoms (SPT, 3 items);
- Relationships with friends (RFr, 4 items);
- Relationships with family (RFa, 3 items);
- Relationship with the healthcare system (RHCS, 3 items);
- Sentimental and sexual life (SSL, 2 items);
- Coping (COP, 2 items); and
- Rejection (REJ, 2 items).

Each item is scored from 1 (never/not at all) to 5 (always/very much) or 6 if not applicable.

Negatively worded item scores are reversed so that higher scores indicated a higher level of quality of life.

All nine dimensions are linearly transformed to a 0 to 100 scale, where 0 indicates the worst possible level of quality of life and 100 indicates the best level. The index score is computed as the mean of these subscales scores.

If fewer than half of the items were missing, the mean of the non-missing items is substituted for the missing items.

The final version of the questionnaire is included in [Appendix 2](#).

MusiQoL evaluation will be done at Baseline Visit, Month 6 and Month 12. Baseline MusiQoL score will be compared with after 6 and 12 months of Rebif treatment.

- Reasons for discontinuation of initial MS treatment

Reasons for discontinuation of initial MS treatment will be collected at Baseline.

- Treatment Adherence

Adherence to Rebif therapy will be collected electronically using RebiSmart 2.0. The data on adherence will be collected after 6 and 12 months of Rebif treatment.

Further details on Endpoints are provided in Section [9.1.2](#).

9.4 Data Source

The data to be collected in the study will be obtained by mean of an electronic case report form (eCRF). Data will be entered into the eCRF by the investigator site staff. Subjects will attend the investigator site for regular visits during their treatment with Rebif according to local clinical practice. Assessments conducted during these visits will be according to clinical practice. [Table 1](#) defines assessments that the Investigator will enter in the eCRF if the assessments have been undertaken during subject visits. Demographic information, MS history, prior and current medication will be captured from the subjects medical records, prescription records, laboratory reports and/or routine interview of patients.

Subjects will complete the MusiQoL and TSQM v II questionnaires and the information will be transcribed into the eCRF by the investigator site staff.

All data collected during the course of this study must be documented in eCRF on an ongoing basis in a complete, accurate, legible and timely fashion. The data in the eCRF should be consistent with the relevant source documents. Further details are provided in Section [9.6](#).

9.5 Study Size

A sample size of 106 subjects will be required to have 85% power to detect at least an 8 point difference in mean TSQM scores between Baseline and Month 6 or Month 12 measurements, with the standard deviation (SD) of 27.5 and a two sided significance level of 5%. Assuming a 20% dropout rate, approximately 133 patients will be enrolled into the study in the Netherlands, Switzerland and Belgium.

9.6 Data Management

The main purpose of the eCRF is to obtain data required by the non-interventional study protocol in a complete, accurate, legible and timely manner. The data in the eCRF should be consistent with the relevant source documents.

Data protection and privacy regulations will be implemented in capturing, forwarding, processing, and storing subject data. Patients will provide written informed consent prior to data abstraction and any data handling procedures in accordance with local regulations.

A unique subject number will be assigned to each participating patient. This number will serve as the patient’s identifier in this observational study database.

The Investigator or designee is responsible for ensuring that the data collected in the course of this study is accurate and documented appropriately on all applicable forms. They will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations. The Investigator must ensure that the eCRFs and any other associated documents forwarded to Sponsor or its designated organization contain no mention of any subject names.

The data will be entered into a validated database. The Sponsor/Contract Research Organization (CRO) or its designee will be responsible for data processing, in accordance with the Sponsor’s/CRO’s data management procedures. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the database. The data management plan will detail the data entry, cleaning, clarification, and validation procedures to be followed by all relevant study staff. Database lock will occur once quality assurance procedures have been completed.

9.7 Data Analysis

All analyses will be performed on subjects who received at least one dose of Rebif following enrollment in the study.

Descriptive statistics (n, mean, SD, median, first quartile [Q1], third quartile [Q3], minimum, maximum) will be provided for continuous variables. Frequencies and percentages will be presented for categorical and ordinal variables.

All data analyses will be performed by the CRO after the study is completed and the database is locked. Statistical programming and analyses will be performed using SAS 9.1.3 (or higher). Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP).

9.7.1 Analysis Sets

Safety Analysis Set:

Safety analysis set is defined as all the subjects who provided informed consent and who received at least one dose of study treatment.

9.7.2 Derived and Transformed Data

Missing information will be captured for quantitative as well as qualitative variables by the category “Missing” in the summary statistics. If there are no missing values this will be indicated by “0” unless otherwise specified. Missing data will not be imputed.

9.7.3 Statistical Methods

The statistical analyses described in this section will be performed as further outlined in the SAP, which will be finalized prior to database lock and will be included in the clinical study report for this protocol. The final SAP will take into account any amendment to the protocol.

General Statistical Methodology:

Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, maximum) will be provided for continuous variables. Frequencies and percentages will be presented for categorical and ordinal variables. Where appropriate, 95% confidence intervals (CIs) will be presented.

All analyses will be performed on safety analysis set.

Primary Endpoint Analysis:

A paired two-sided t-test of the global satisfaction score (TQSM score) will be used to test the null hypothesis that there is no difference in the global satisfaction score (TQSM score) between 6, 12 months and Baseline. The corresponding 95% two-sided CI will be presented.

Secondary Endpoints Analyses:

ARR and its associated 95% CI before study entry and after 12 months of Rebif treatment will be summarized overall and by previous MS therapy.

Reasons for discontinuation of previous therapy and adherence after 6 and 12 months of Rebif treatment will be summarized descriptively and overall.

Changes in MusiQoL after 6 and 12 months of Rebif treatment versus Baseline will be analysed using same methodology as for Primary Endpoint.

Analysis of additional Secondary Endpoints as correlation analysis between TSQM and MusiQoL versus ARR, adherence and reason for discontinuation will be described in the SAP.

9.7.4 Sequence of Analyses

No interim analysis will be carried out for this study.

9.8 Quality Control

9.8.1 Monitoring

Risk based monitoring will be performed for this study. Risk based monitoring is the process of ensuring the quality of clinical trials by identifying, assessing, monitoring and mitigating the risks that could affect the quality or safety of a study. It can facilitate efficient trial delivery without compromising patient safety or data quality. A Sponsor or an appointed CRO will identify critical data and processes, performs a risk assessment and then develops a monitoring plan that focuses on the important and likely risks to critical data and processes.

A Sponsor or an appointed CRO Monitor may perform visits to the site, if required, at any time during the study. For hospitals where potential quality risks are identified, on-site visits can verify that the study is being carried out according to the protocol.

9.8.2 Archiving

The archive should be maintained for the period specified by local regulations, where applicable. All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations. In the absence of applicable regulations, the archive should be maintained for at least 5 years after the final study report or the first publication of study results, whichever comes later. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

9.8.3 Quality Assurance and Audit

In compliance with regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, regulatory agencies, or IEC/IRB may conduct quality assurance audits/inspections at any time during or following a study. The Investigator must agree to allow auditors/inspectors direct access to all study related documents, including source documents, and must agree to allocate his or her time and the time of his or her study staff to the auditors/inspectors in order to discuss findings and issues.

The protocol, each step of the data capture procedure, and the handling of the data, as well as the eventual study report, will be subject to independent clinical quality assurance. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

9.9 Limitations of the Research Methods

This study is open label and observational, and therefore has inherent limitations in terms of susceptibility to bias, confounding and restricting the ability to define causality. There is limited control over patient assessment as patient monitoring and diagnostics are per standard of care; no additional clinical monitoring is generally conducted. Patient specific methodological challenges such as potential biases from patient selection, loss of patients through study attrition, and overall patient recall are also other limitations. However, observational study strengths include that they

reflect daily clinical practice more closely than randomized controlled trials, both in terms of the heterogeneous patient populations that are included, and the medical interventions that they receive. Real-life observational data is essential to assess and improve clinical practice worldwide and complement randomized controlled trials by providing clinically-relevant, real-world data and provide considerable health economic information.

9.10 Other Aspects

None

10 Protection of Human Subjects

10.1 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the study at a given site, the protocol will be submitted together with its associated documents (subject information and ICF in the languages to be used) to the responsible IEC/IRB for its favorable opinion/approval. The written favorable opinion/approval of the IEC/IRB will be filed by the Investigator and a copy will be sent to the Sponsor.

The study must not start at a site before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IEC/IRB. The IEC/IRB will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given, and of the members and voting members present at the meeting. Written evidence of favorable opinion/approval that clearly identifies the study, the protocol version, and the subject information and consent form version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to the protocol will also be submitted to the concerned IEC/IRB, before implementation in case of substantial changes.

10.2 Subject Information and Informed Consent

An unconditional prerequisite for a subject's participation in the study is his/her written informed consent. The subject's written informed consent to participate in the study must be given before any study related activities are carried out.

Adequate information must therefore be given to the subject by the Investigator before informed consent is obtained (a person designated by the Investigator may give the information, if permitted by local regulations). A subject information sheet in the local language will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or his/her designee will inform the subject verbally of all pertinent aspects of the study (the language used in doing so must be chosen so that the information can be fully and readily understood by laypersons). Depending on

national regulations, a person other than the Investigator may inform the subject and sign the ICF.

The ICF must be signed and personally dated by the subject and the Investigator. The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived by the Investigator. A copy of the signed and dated information and consent form should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to the subject's consent, the written subject information sheet and any other written information provided to subjects will be revised by the Sponsor and be submitted again to the IEC/IRB for review and favorable opinion. The agreed, revised information will be forwarded to each subject in the study. The Investigator will explain the changes to the previous version.

10.3 Subject Identification and Privacy

A unique subject number will be assigned to each subject at inclusion. This number will serve as the subject's identifier in the study as well in the study database.

The Investigator must ensure that the subjects' anonymity is maintained. On the case report forms (CRFs) or other documents submitted to the Sponsor, subjects should not be identified by their names, but by their assigned identification numbers. If subject names are included on copies of documents submitted to the Sponsor, the names (except for initials) must be obliterated and the assigned subject numbers added to the documents.

The Investigator should keep a separate log of subjects' identification numbers, names, addresses, telephone numbers and hospital numbers (if applicable). Documents not for submission to the Sponsor, such as signed ICFs, should be maintained in strict confidence by the Investigator.

Only authorized persons will have access to identifiable personal details, if required for data verification. The subject's original medical data that are reviewed at the site during source data verification by the Monitor, audits, and Health Authority inspections will be kept strictly confidential. The Investigator agrees to provide direct access to these documents to the Sponsor and to Health Authority representatives. The Investigator is responsible for retrieving information from personal medical records.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

10.4 Health Authorities

The protocol and any applicable documentation (subject information and consent form) will be submitted or notified to the National Health Authorities in accordance with the regulations of the country or countries involved in the study.

11 Management and Reporting of Adverse Events

Safety of Rebif will mainly be evaluated by the recording of all AEs.

11.1 Adverse Events

Adverse Event

An AE is any untoward medical occurrence in a patient or clinical study subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Reaction

An AR is a response to a medicinal product which is noxious and unintended.

Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.

ARs may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.

Serious Adverse Event/Serious Adverse Reaction

A SAE/reaction is any AE/AR as defined above, which also fulfills at least one of the seriousness criteria below:

- Results in death
- Is life-threatening¹⁾
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is otherwise considered as medically important²⁾

¹)Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

²)Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious AR.

Events not to be considered as AEs

Medical conditions present at study start, that do not worsen in severity or frequency during the study are defined as Baseline medical conditions, and are NOT to be considered AEs.

11.2 Severity of Adverse Events

Investigators should assess the severity/intensity of any AEs as follows:

- Mild:** The subject is aware of the event or symptom, but the event or symptom is easily tolerated.
- Moderate:** The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.
- Severe:** Significant impairment of functioning: the subject is unable to carry out usual activities.

11.3 Causality Assessment

Investigators must assess the causal relationship between AEs and study drug (including any other non-medicinal product, radiation therapy, etc.) considering temporal relationship between the AE onset and study drug administration, safety profile of study drug (known side effects), the patient's condition (medical history, underlying disease), concomitant medication, and study procedures.

Related: Suspected to be reasonably related to any study medication.

Not related: Not suspected to be reasonably related to any study medication. A reasonable alternative explanation must be available.

11.4 Recording of Adverse Events in the Case Report Form

The recording period for AEs begins, when the subject is initially included in the study (date of signature of first informed consent) and continues until the End of the Study (Visit 3 or premature withdrawal).

All SAEs (related and not related) and non SAEs (related AEs) must be collected in the eCRF.

Each AE, as specified above, occurring during the study, must be documented by the Investigator within 24 hours of awareness and must be recorded in the eCRF, including its description, severity, duration (onset and resolution dates), causal relationship (i.e., confirmation that the AR is suspected to be reasonably related to the study treatment), any other potential causal factors, actions taken with the study drug (dose reduction, withdrawal), required treatment, and outcome. In addition, for all serious ARs, seriousness criteria must be documented and a specific safety report form must be completed and sent to the Sponsor, as described below

Death, disability, and hospitalization are considered outcomes in the context of safety reporting and not usually considered ARs/AEs. Therefore the primary cause of death, disability or hospitalization should be recorded and reported as an SAE/AR, and the outcome should be recorded in a separate data field. However, a term for the outcome will be selected if it is the only information reported or provides significant clinical information.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. “Fatal” will be recorded as the OUTCOME of this respective event and not be as separate event. Only, if no cause of death can be reported (for example, sudden death, unexplained death), the death per se might then be reported as an SAE.

Medication Errors, Overdose, Abuse, and Misuse

Events of medication errors, overdose, abuse and misuse of study drug are also to be recorded in the eCRF, even if occurring without AE.

Pregnancy and Lactation

If encountered on this study exposure to study drug during pregnancy or lactation is to be recorded in the eCRF and to be reported to the study sponsor.

11.5 Safety Reporting to the Study Sponsor

Safety data collection forms:

The following safety data collection forms are used in this study:

- SAE Report Form
- Pregnancy Report Form
- Parent-Child/Foetus AE Report Form

Reportable events:

The following events are reportable to the Safety Check Desk at CRO within 24 hours of awareness:

- All SAEs (related or unrelated) are to be reported independent of their relationship to the study drug by using the SAE report form.
- Non-serious ARs^{*)}
- Pregnancies to be reported independent of the relationship to an AE by using the Pregnancy Report Form.
- All events that occur in a Child/Foetus of a pregnant woman who was exposed to the study drug are to be reported by using the Parent-Child/Foetus Report Form
- Special considerations including medication errors, overdose, abuse, misuse; exposure during pregnancy and/or lactation should be reported on the SAE report form by indicating whether serious or not.

*) All non-serious suspected adverse drug reactions (related to any study medication) only need to be recorded in the eCRF; those are downloaded daily by the Sponsor into the Sponsor Global Drug Safety Database.

Procedure for Safety Data Reporting (completion and forwarding):

In the event of any new safety data that have to be reported as specified above, the Investigator must immediately (within 24 hours after becoming aware of the event) inform the Sponsor or its designee. For all events that require a written form to the Sponsor, the Investigator completes the respective Safety Data Collection Form within 24 hours in English and sends the report by email or fax to the CRO Safety Check Desk. The Investigator must respond to any request by CRO for follow-up information within the same timeline as noted above for initial reports for further forwarding the report to the Global Drug Safety. The sponsor has to meet strict regulatory timelines associated with expedited safety reporting obligations.

CRO Safety Check Desk:

- Email: *CRO mailbox address, ideally as per project*
- Fax: *CRO Fax number, ideally as per project*

Global Drug Safety:

- Email: PPD [REDACTED]
- Fax: PPD [REDACTED]

The data entered on the safety data collection forms must be consistent with the information recorded in the eCRF. If some data are missing, the form should be completed with the available

data and a follow-up report will be sent as soon as possible. The minimum information to be included in the initial report is the following:

- Investigator name and contact details
- Subject identification (e.g., ID number, sex, age)
- Product (including lot/ batch number)
- Description of SAE/ Adverse Drug Reaction/ Special considerations

The report should contain causality and seriousness information (for AEs) and must be signed off by the Investigator.

When AE information is communicated via telephone, a written/electronic data capture (EDC) report must be sent immediately within 24 hours thereafter by fax or e-mail. In such cases the “clock start” for case reporting to Health Authorities is the date and time of the telephone communication.

Exposure during Pregnancy

All pregnancies with an estimated conception date in the period from the date of informed consent signature (where applicable) until the last post-treatment safety visit, or as defined in the protocol, must be recorded by convention in the AE page/section of the eCRF. The same rule applies to pregnancies in female subjects and to pregnancies in female partners of male subjects. The Investigator must notify the Sponsor in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting. The Sponsor must be notified about any pregnancy independent whether the pregnancy is associated with an AE or not.

Investigators must actively follow up, document, and report to the Sponsor on the outcome of all these pregnancies and deliveries even if the subject is withdrawn from the study. If an abnormal outcome occurs, the respective safety data collection form (Pregnancy Report Form, Parent-Child/Foetus AE Report Form) is to be completed and sent to the Sponsor.

Procedure for Follow-up information

The Investigator must promptly respond to any request for follow-up information or questions from the Sponsor or delegate (e.g. CRO). Such requests will be sent to the Investigator via the CRO Safety Check Desk. SAEs occurring during the study must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is lost to follow-up.

The Investigator will ensure any necessary additional therapeutic measures and follow-up procedures are recorded and reported via a follow-up report form. For all serious cases missing information such as outcome, confounders, and causality is to be provided. Additionally, follow-up information of non-serious adverse drug reactions may be required by the Sponsor for

medical assessment. Reasonable attempts to obtain follow-up information must be made and documented.

Reporting of any new information on a previously reported SAE or non-serious adverse drug reaction (follow-up) will follow the procedures and timelines of the original report.

11.6 Regulatory Reporting to the Health Authorities

Expedited reporting of SAEs and non-serious adverse drug reactions to Health Authorities is performed by the Sponsor local drug safety officer/Pharmacovigilance responsible at shared service center according to applicable global and local requirements.

Serious ARs, including those associated with the comparator drug (if applicable), will be expedited by the Sponsor to Health Authorities according to local regulations, which usually require a maximum period of 15 days.

In addition, the Investigator will comply with any applicable local pharmacovigilance requirements to report appropriate safety data, to national pharmacovigilance systems (e.g. Yellow Card Scheme in UK), as required by country specific reporting requirements.

12 Plans for Disseminating and Communicating Study Results

After completion of the study, the selected CRO shall prepare a final report of study results, in close collaboration with the coordinating Investigator and the Sponsor.

All publications and presentations should be based on the final study report.

All information provided by the Sponsor regarding this study will be the sole property of the Sponsor and must be considered as confidential. No confidential information will be disclosed to third parties without the prior written consent of the Sponsor and it will be used only for conducting this study.

12.1 Study Report(s)

The completed study will be summarized in a final report that accurately and completely presents the study objectives, methods, results, limitations of the study, and interpretation of the findings.

12.2 Publication

The first publication will be a publication of the results of the analysis of the Primary Endpoint that will include data from all study sites.

The Investigator will inform the Sponsor in advance about any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require pre-submission review and approval by the Sponsor.

The Sponsor will not suppress or veto publications, but maintains the right to delay publication in order to protect intellectual property rights.

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14 Appendices

1. Appendix 1: TSQM Version II Questionnaire

Treatment Satisfaction Questionnaire for Medication (TSQM) Version II

Instructions:

Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical study. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication over the last two to three weeks, or since you last used it. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat the condition?

☐1 Extremely Dissatisfied

☐2 Very Dissatisfied

☐3 Dissatisfied

☐4 Somewhat Satisfied

☐5 Satisfied

☐6 Very Satisfied

☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves symptoms?

☐1 Extremely Dissatisfied

☐2 Very Dissatisfied

☐3 Dissatisfied

☐4 Somewhat Satisfied

☐5 Satisfied

☐6 Very Satisfied

☐7 Extremely Satisfied

3. As a result of taking this medication, do you experience any side effects at all?

☐1 Yes

☐0 No

4. How dissatisfied are you by side effects that interfere with your physical health and ability to function (e.g., strength, energy levels)?

☐1 Extremely Dissatisfied

☐2 Very Dissatisfied

☐3 Somewhat Dissatisfied

☐4 Not Applicable

☐5 Slightly Dissatisfied

☐6 Not at all Dissatisfied

5. How dissatisfied are you by side effects that interfere with your mental function (e.g., ability to think clearly, stay awake)?

☐1 Extremely Dissatisfied

☐2 Very Dissatisfied

☐3 Somewhat Dissatisfied

☐4 Slightly Dissatisfied

☐5 Not at all Dissatisfied

6. How dissatisfied are you by side effects that interfere with your mood or emotions (e.g., anxiety/fear, sadness, irritation/anger)?

☐1 Extremely Dissatisfied

☐2 Very Dissatisfied

☐3 Somewhat Dissatisfied

☐4 Slightly Dissatisfied

☐5 Not at all Dissatisfied

7. How satisfied or dissatisfied are you with how easy the medication is to use?

☐1 Extremely Dissatisfied

☐2 Very Dissatisfied

☐3 Dissatisfied

☐4 Somewhat Satisfied

☐5 Satisfied

☐6 Very Satisfied

☐7 Extremely Satisfied

8. How satisfied or dissatisfied are you with how easy it is to plan when you will use the medication each time?

☐1 Extremely Dissatisfied

☐2 Very Dissatisfied

☐3 Dissatisfied

☐4 Somewhat Satisfied

☐5 Satisfied

☐6 Very Satisfied

☐7 Extremely Satisfied

9. How satisfied or dissatisfied are you by how often you are expected to use/take the medication?

☐1 Extremely Dissatisfied

☐2 Very Dissatisfied

☐3 Dissatisfied

☐4 Somewhat Satisfied

☐5 Satisfied

☐6 Very Satisfied

☐7 Extremely Satisfied

10. How satisfied are you that the good things about this medication outweigh the bad things?

☐1 Extremely Dissatisfied

☐2 Very Dissatisfied

☐3 Dissatisfied

☐4 Somewhat Satisfied

☐5 Satisfied

☐6 Very Satisfied

☐7 Extremely Satisfied

11. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied

☐2 Very Dissatisfied

☐3 Dissatisfied

☐4 Somewhat Satisfied

☐5 Satisfied

☐6 Very Satisfied

☐7 Extremely Satisfied

SCALE SCORING ALGORITHM: TSQM Scale scores range from 0 to 100 and no computed score should be lower or higher than these limits.

EFFECTIVENESS: $\frac{[(\text{Item 1} + \text{Item 2}) - 2]}{(12)} \times 100$

SIDE EFFECTS: $\frac{[(\text{Sum of Item 4 to Item 6}) - 3]}{(12)} \times 100$

If one item is missing: $\frac{[(\text{Sum of the two completed items}) - 2]}{(8)} \times 100$

CONVENIENCE: $([\text{Sum of Item 7 to Item 9}] - 3) \text{ divided by } 18) \times 100$

If one item is missing: $([(\text{Sum of the two completed items}) - 2] \text{ divided by } (12) \times 100$

GLOBAL SATISFACTION: $([\text{Sum of Item 10 to Item 11}] - 2) \text{ divided by } 12) \times 100$

2. Appendix 2: Multiple Sclerosis International Quality of Life (MusiQoL) Questionnaire

Quality of Life Questionnaire: MusiQoL Version 5.4

You are invited to complete this questionnaire concerning different aspects of your life with MS. It is anticipated that this will help towards a better understanding of the real impact of your health problems.

Please answer the questions by ticking (✓) or checking (☒) the box that describes best your feelings during the last 4 weeks.

Some questions relate to your private life; these are necessary to evaluate all aspects of your health. However, if you think that a question is not relevant to you, or if you do not want to answer a question, please move on to the next one.

Due to your MS, during the past 4 weeks, have you...						
For each question, check the response that is closest to your feelings		Never Not at all	Rarely A little	Sometimes Somewhat	Often A lot	Always Very much
1	Had difficulty walking or moving outside?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	Had difficulty with outdoor activities: i.e. shopping, going out to a movie?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	Had difficulty walking or moving around at home?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4	Been troubled by your balance or walking problems?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5	Had difficulty with leisure activities at home: i.e. do-it-yourself, gardening?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6	Had difficulty with your occupational activities: i.e. integration, interruption, limitation?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7	Been quickly tired?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8	Been short of energy?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9	Felt anxious?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10	Felt depressed or gloomy?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11	Felt like crying?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12	Felt nervous or irritated by a few things or situations?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Due to your MS, during the past 4 weeks, have you...						
For each question, check the response that is closest to your feelings		Never Not at all	Rarely A little	Sometimes Somewhat	Often A lot	Always Very much
13	Been troubled by loss of memory?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14	Had difficulty concentrating: i.e. when reading, watching a film, following a discussion?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15	Been troubled by your vision: worsened or unpleasant?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16	Experienced unpleasant feelings: i.e. hot, cold?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17	Talked with your friends?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18	Felt understood by your friends?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19	Felt encouraged by your friends?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20	Talked with your spouse/partner or your family?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21	Felt understood by your spouse/partner or your family?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22	Felt encouraged by your spouse/partner or your family?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Due to your MS, during the past 4 weeks, have you...						
For each question, check the response that is closest to your feelings		Never Not at all	Rarely A little	Sometimes Somewhat	Often A lot	Always Very much
23	Felt satisfied with your love life?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
24	Felt satisfied with your sex life?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
25	Felt that your situation is unfair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
26	Felt bitter?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
27	Been upset by the stares of other people?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
28	Been embarrassed when in public?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
29	Been satisfied with the information on your disease or the treatment given by the doctors, nurses, psychologists... taking care of your MS?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
30	Felt understood by the doctors, nurses, psychologists... taking care of your MS?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
31	Been satisfied with your treatments?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

15

Annexes

None

15.1 Signature pages and responsible persons for the study

Signature Page – Protocol Lead

Study Title: A Phase IV, prospective, multicenter, open label, uncontrolled, non-interventional, single arm study to measure treatment satisfaction of multiple sclerosis (MS) patients on Rebif after discontinuing initial first-line treatment

Study Protocol Date / Version: 10 Oct 2016 / Version 2.0

Protocol Lead responsible for designing the non-interventional study:

I approve the design of the non-interventional study protocol:

Signature

Date of Signature

Name, academic degree: _____
Function / Title: _____
Institution: Merck B.V.,
Address: Tupolevlaan 41-61,
1119 NW Schiphol-Rijk,
The Netherlands.
Telephone number: _____
Fax number: _____
E-mail address: _____

Signature Page –Coordinating Investigator

Study Title: A Phase IV, prospective, multicenter, open label, uncontrolled, non-interventional, single arm study to measure treatment satisfaction of multiple sclerosis (MS) patients on Rebif after discontinuing initial first-line treatment

Study Protocol Date / Version: 10 Oct 2016 / Version 2.0

I approve the design of the non-interventional study and I understand and will conduct the study according to the study protocol, any approved protocol amendments, Good Pharmacovigilance Practices (GPP) and all applicable Health Authority requirements and national laws.

Signature

Date of Signature

Name, academic degree: PPD

Function / Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

PPD

Signature Page – Principal Investigator

Study Title

A Phase IV, prospective, multicenter, open label, uncontrolled, non-interventional, single arm study to measure treatment satisfaction of multiple sclerosis (MS) patients on Rebif after discontinuing initial first-line treatment

Study Protocol Date / Version

07 Oct 2016 / Version 2.0

Center Number

Principal Investigator

I, the undersigned, am responsible for the conduct of the study at this site and affirm that I understand and will conduct the study according to the study protocol, any approved protocol amendments, Good Pharmacovigilance Practices (GPP) and all applicable Health Authority requirements and national laws.

Signature

Date of Signature

Name, academic degree:

Function / Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address: